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(54) Method for calibration and measurement in a micro-dialysis system

(57) A method for calibration and measurement of a micro-dialysis system, comprising one sensor (14, 16), is described. Measurement times in micro-dialysis tend to be long, since concentration equilibrium at the measurement probe is necessary. The method is devised to enable calibration and measurement to be performed with two dialysates with differing analyte contents in order to facilitate measurement with no need to wait for complete equilibrium.

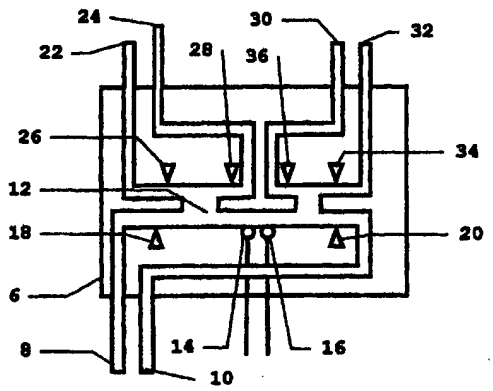

FIG. 2

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Description

[0001] The present invention relates to a method for calibration and measurement in a micro-dialysis system according to the preamble to claim 1.

[0002] The present invention also relates to a micro-dialysis system according to the preamble of claim 4.

[0003] In micro-dialysis a measurement probe is inserted into the measurement area, usually a part of a patient's body. The measurement probe contains a dialysate that, through a permeable part of the measurement probe, accepts substances diffusing out of the measurement area. The substances can consist of e.g. oxygen ions in blood. The dialysate is subsequently carried to a sensor for measuring the diffusing substance. This provides a measure of a specific parameter in the measurement area, e.g. the blood gas value for oxygen.

[0004] One problem in this procedure is to ensure that the sensor measures a relatively correct value. If the sensor does not measure a direct value, it should be possible to at least calculate the correct value.

[0005] In principle, two factors have a predominant impact on sensor accuracy: the measurement probe's recovery ability and the sensor's signal drift.

[0006] Recovery ability R is defined as

$$R = \frac{C_{dialysate}}{C_{measurement\ area}}$$

where C stands for the concentration of the diffusing substance (in the dialysate and measurement area respectively).

[0007] Recovery ability depends, in turn, on factors such as temperature, the material the measurement probe is made of, the flow of dialysate and convection around the measurement probe. Several of these factors vary with time, and the system must operate very slowly, or recovery must be monitored in some way, to assure 100% recovery between each measurement. If recovery is monitored, a calculation can be made to compensate for measurements made before 100% recovery has taken place.

[0008] One objective of the invention is to achieve a method for micro-dialysis which resolves the aforementioned problems.

[0009] Another objective of the invention is to achieve a micro-dialysis system capable of performing measurements more rapidly and accurately than known micro-dialysis systems.

[0010] The first objective is achieved according to the invention when the method is devised with the method steps that are evident from the characterising part to claim 1.

[0011] Advantageous embodiments of the method are evident from the dependent claims to claim 1.

[0012] A more effective analysis method can be employed when two dialysates, with differing analyte contents in respect to the parameter to be identified, are used. The two dialysates are employed in such a way that calibration and measurement are performed with one dialysate at a time. The first dialysate is used at appropriate intervals, preferably for every second calibration and measurement. The second dialysate is used for the remaining calibrations and measurements.

[0013] 100% recovery is then no longer necessary, since two-point calibration of the sensor becomes possible. This, combined with utilisation of the three most recent measurements for determining the measurement value, two calibrations and the actual measurement.

[0014] The second objective is achieved according to the invention when the micro-dialysis system is devised as is evident from the characterising part to claim 4.

[0015] The micro-dialysis system is devised to enable two dialysates to be used alternately in some suitable fashion for performing the method described above.

[0016] The method and the micro-dialysis system according to the invention will be described below in greater detail, referring to the following figures.

FIG. 1 is a diagram illustrating the course of recovery for two dialysates;

FIG. 2 is a schematic depiction of a first embodiment of a measurement cassette in a micro-dialysis system according to the invention; and

FIG. 3 is a schematic depiction of a second embodiment of a measurement cassette in a micro-dialysis system according to the invention.

[0017] In micro-dialysis, a measurement probe is inserted into a measurement field, as a rule by invasive introduction into a patient. A typical example of this is insertion into a patient's vein or artery for the purpose of measuring blood gases. The measurement probe is filled with a dialysate. Gas molecules, e.g. oxygen, in the measurement probe's surroundings diffuse into the measurement probe. When equilibrium has been reached, the concentration of the gas molecules in the measurement area can be measured by measuring the concentration in the dialysate. Measurement is performed by a sensor.

[0018] As is the case with most types of measurement equipment, the micro-dialysis system is subject to signal drift which can lead to erroneous measurement results. Two factors are mainly found in micro-dialysis systems. Signal drift in the sensor, and the measurement probe's recovery time.

[0019] Signal drift in the sensor can be remedied with recurrent calibration during operations. Calibration must then be performed at a known concentration.

[0020] Recovery time for the probe is more complex. In concrete terms, this means that concentration

equilibrium must be complete before the dialysate can be sent from the probe to the sensor. A number of factors affect this. The temperature, the material the measurement probe is made of, the flow of dialysate, convection in the measurement area etc. A plurality of these factors also change over time. All told, this means that the micro-dialysis system must normally operate slowly to keep measurement results from being compromised.

[0021] This problem is solved with the present invention by utilisation of two dialysates with different analyte contents. These dialysates are employed in achieving two-point calibration of the sensor.

[0022] The dialysates are utilised alternately, i.e. first calibration and measurement with one dialysate and then calibration and measurement with the other dialysate. When the last two calibrations are utilised with the latest measurement, correct measurement values can be obtained with no need to take the measurement probe's recovery time into account.

[0023] FIG. 1 is a diagram showing concentration curves for a first dialysate 2 and a second dialysate 4. The y axis shows the concentration, and the x axis shows the time in minutes. With the designation C_1 for the concentration of the first dialysate, C_2 for the concentration of the second dialysate and C_x for the concentration in the measurement area, the following relationships can be established for the concentrations's variation in the measurement probe:

$$C_{1x} = C_1 + (C_x - C_1)(1-e^{-\alpha t}) \quad [1]$$

$$C_{2x} = C_2 + (C_x - C_2)(1-e^{-\alpha t}) \quad [2]$$

[0024] α is a diffusion constant and t designates the time. At time zero the respective dialysate 2, 4 has an opening concentration of C_1 and C_2 respectively. The concentration then decreases (for the first dialysate, corresponding to C_{1x}) and increases (for the second dialysate, corresponding to C_{2x}) exponentially with time, achieving after about 5 minutes the concentration C_x (at which equilibrium prevails) of the surroundings (measurement area).

[0025] It should be emphasised that the diagram shows a concrete example of the variation in concentration. The time elapsing until equilibrium occurs can therefore vary considerably, depending on the circumstances.

[0026] A reasonable assumption is that the sensor displays, or can be made to display, a linear correlation between the concentration and output voltage. When calibrations are at least performed with the same dialysate flow, the corresponding chronological course will take place in the measurement probe. It is also reasonable to expect the time constant, temperature and other factors not to change drastically. They can therefore be viewed as constants over at least two calibration procedures.

[0027] The equations [1] and [2] then only contain two unknowns, viz, the diffusion constant α and the equilibrium concentration C_x. These equations can them be merged to form the following relationship:

$$C_X = \frac{C_1(C_{2x} - C_2) - C_2(C_{1x} - C_1)}{C_{2x} - C_2 - C_{1x} + C_1} \quad [3]$$

[0028] The output signals from the sensor are voltages and can be designated U_{1x} and U_{2x} for unknown concentrations (U_1 is obtained for the first dialysate at the concentration C_1 and U_2 for C_2). With the aforementioned assumptions that the sensor displays a linear correlation and that the parameters can be regarded as constants over short intervals, the following transfer function is obtained for the sensor's output signal:

$$U = U_1 + \frac{U_2 - U_1}{C_2 - C_1}(C - C_1) \quad [4]$$

[0029] With this transfer function, equations [1] and [2] can be expressed as:

$$C_{1x} = C_1 + \frac{C_2 - C_1}{U_2 - U_1}(U_{1x} - U_1) \quad [5]$$

$$C_{2x} = C_2 + \frac{C_2 - C_1}{U_2 - U_1}(U_{2x} - U_1) \quad [6]$$

[0030] Utilisation of the equations [3], [5] and [6] makes it possible to calculate the unknown concentration C_x of a sample from the known concentrations C_1, C_2 in the dialysate, the two calibrations U_1, U_2 and the two measurements U_{1x}, U_{2x}.

[0031] The system therefore automatically compensates for all slow signal drifting.

[0032] Constant utilisation of preceding measurements results in a faster system, relatively speaking. (Two measurements and two calibrations are only required initially before calculations can start as above.)

[0033] FIG. 2 schematically depicts a measurement cassette 6 in a micro-dialysis system in which measurement is performed in the measurement cassette 6.

[0034] A dialysate from a measurement probe (not shown) enters the measurement cassette 6 for measurement through a first inlet 8. At the same time, dialysate is sent to the measurement probe through a first outlet 10. The dialysate is sent to a test chamber 12 and comes into contact with a first sensor 14 and a second sensor 16 for e.g. determination of the concentration of oxygen ions in the dialysate.

[0035] The flow to and from the measurement

probe can be stopped with a first valve 18 and a second valve 20. The measurement probe should be devised to enable dialysate to flow in both directions, i.e. not only in through the inlet 8 and out through the outlet 10 but the reverse as well.

[0036] A first calibration dialysate can be fed into the measurement chamber 12, through a second inlet 22, for calibration of the sensors 14, 16 at a first specific concentration. The first calibration dialysate can be carried out of the measurement cassette 6 through a second outlet 24.

[0037] The flow of the first calibration dialysate can be stopped with a third valve 26 and a fourth valve 28.

[0038] In the corresponding fashion, a second calibration dialysate can be fed into the measurement chamber 12, through a third inlet 30, for calibration of the sensors 14, 16 at a second specific concentration. The second calibration dialysate can be carried out of the measurement cassette 6 through a third outlet 32.

[0039] The flow of the second calibration dialysate can be stopped with a fifth valve 34 and a sixth valve 36.

[0040] During operation the first calibration dialysate is first carried to the measurement chamber 12 for a first calibration of the sensors 14, 16. An amount of the first calibration dialysate, which is also sufficient to fill the measurement probe, must also be supplied. The sensors 14, 16 are calibrated thereupon.

[0041] After a certain amount of time, the first calibration dialysate can be recovered from the measurement head for measurement of the unknown concentration.

[0042] In the corresponding manner, the second calibration dialysate is then carried into the measurement chamber 12 and the measurement probe for a second calibration and measurement.

[0043] The determination procedure has already been described above.

[0044] FIG. 3 shows an alternative design for the measurement cassette 6 in a second embodiment. The same designations are used for identical components. The measurement cassette 6 comprises a first inlet 8 and a first outlet 10 which leads to a measurement chamber 12 in the measurement cassette 6. Sensors 14, 16 are arranged in the measurement chamber to measure concentration. A first valve 18 and a second valve 20 can stop flow in the measurement probe.

[0045] A first calibration dialysate from a first source 40 or a second calibration dialysate from a second source 42 can be added through a second inlet 38. Dialysate is returned to the respective source 40, 42 through a second outlet 44.

[0046] Switching to the respective dialysate and control of flow through the measurement chamber 12 is by means of a third valve 46, a fourth valve 48, a fifth valve 50, a sixth valve 52, a seventh valve 54 and an eighth valve 56.

Claims

1. A method for calibration and measurement of a micro-dialysis system, comprising a sensor, **characterised** in that calibration and measurement ar performed with two dialysates containing different analytes.

2. The method according to claim 1, **characterised** in that each measurement of a specific sensor parameter is preceded by no more than one calibration measurement using one of the dialysates, the two dialysates being alternately utilised according to a predefined pattern, a pattern controlled by certain criteria or by a combination of the two.

3. The method according to claim 1 or 2, **characterised** in that every other calibration measurement is performed with the respective dialysate.

4. The method according to any of the above claims, **characterised** in that determination of the parameter is made from measurement of the parameter and the two preceding calibration measurements.

5. A micro-dialysis system comprising at least one sensor (14, 16) and a first dialysate intended for calibration of the sensor and measurement of one parameter in a measurement area to which the system is connected, **characterised** in that the system comprises a second dialysate and is devised to perform the method according to any of claims 1-4.

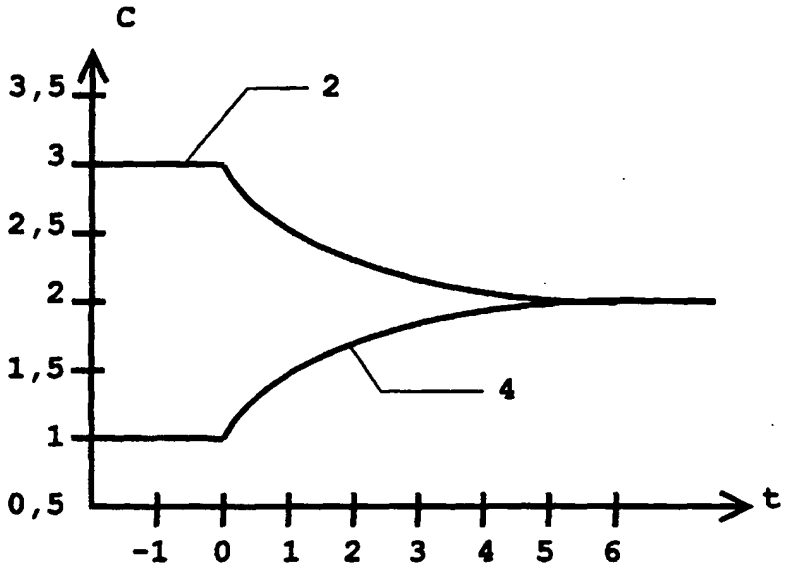
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FIG. 1

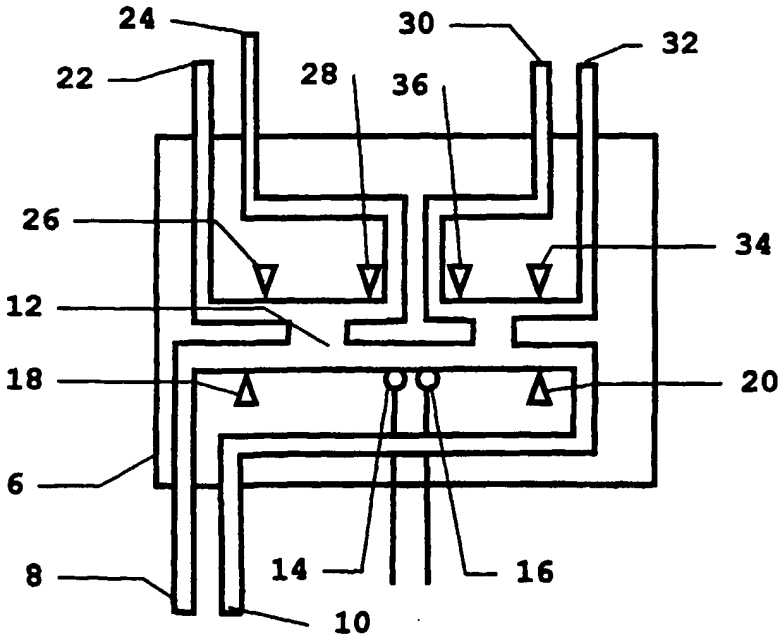
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FIG. 2

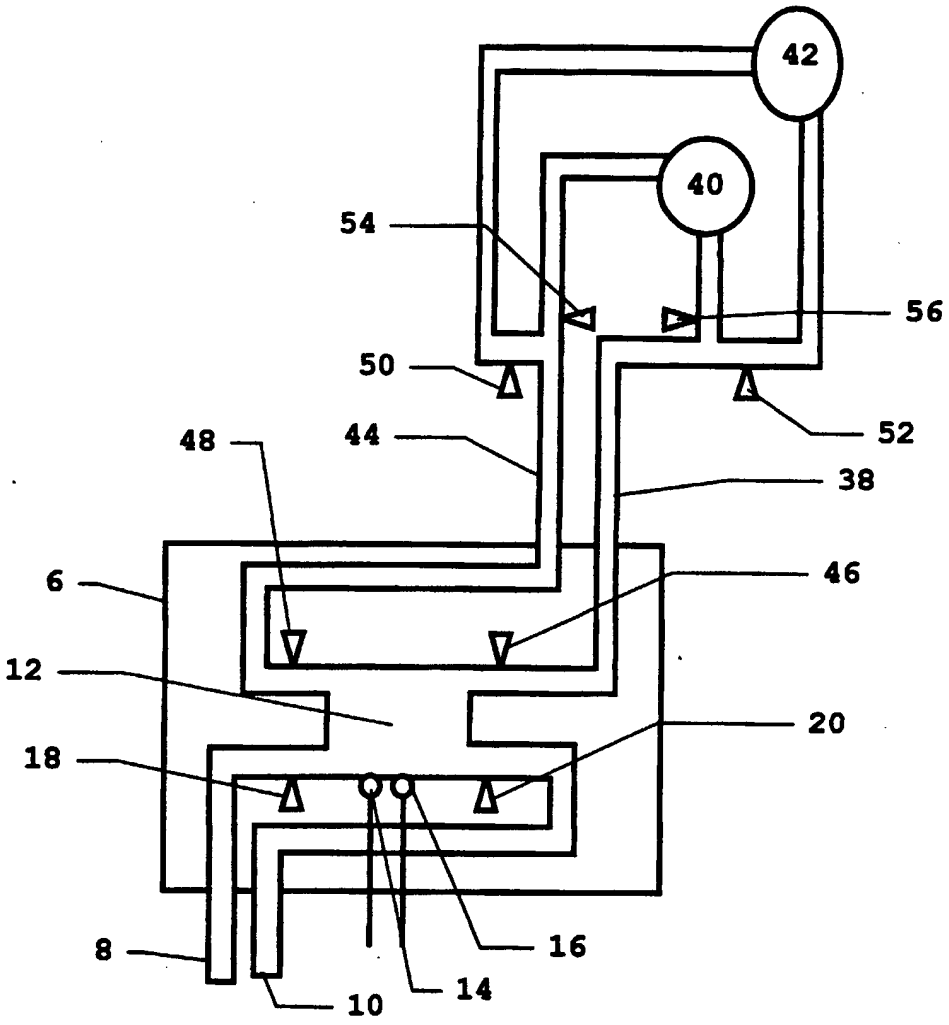

FIG. 3

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EUROPEAN SEARCH REPORT

Application Number
EP 99 11 8198

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Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
Y	US 4 221 567 A (CLARK ET AL.) 9 September 1980 (1980-09-09)	1	A61B5/00
A	* figure 1 * * column 4, line 5 - column 7, line 28 *	2,5	
Y	WO 92 18832 A (OPTEX BIOMEDICAL, INC.) 29 October 1992 (1992-10-29) * page 6, line 2 - page 8, line 8 * * figures 1A-2B *	1	
A	US 5 763 760 A (GUMBRECHT ET AL.) 9 June 1998 (1998-06-09) * column 5, line 42 - column 6, line 67 * * column 7, line 32 - column 14, line 3 * * figures *	1,2,5	
A	GUMBRECHT ET AL.: "Integrated pO2, pCO2, pH sensor system for online blood monitoring" SENSORS AND ACTUATORS B, vol. b19, no. 1-3, April 1994 (1994-04), pages 704-708, XP002900123 CH * the whole document *	1,2,5	TECHNICAL FIELDS SEARCHED (Int.Cl.7) A61B G01N
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The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	31 January 2000	Chen, A

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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